Does rheumatoid factor protect lupus patients from the development of nephritis?

L TURNER-STOKES,¹ M JONES,¹ I ADDISON,² M MANSELL,³ AND D A ISENBERG¹

From the ¹Bloomsbury Rheumatology Unit, the ²Departments of Rheumatology Research and Haematology, University College and the Middlesex Hospital School of Medicine, London, and the ³Institute of Nephrology, St Philip's Hospital, London

SUMMARY It has been suggested again recently that the presence of rheumatoid factor (RF) in the serum of patients with systemic lupus erythematosus (SLE) protects them from the development of nephritis. In this study the RF is measured by standard latex test and by radioimmunoassay to detect IgM, IgA, and IgG isotypes, in patients with SLE with (26 patients) and without (25 patients) renal involvement, and in a control group of 21 patients with idiopathic renal disease. In addition, patients with SLE and nephritis were tested during active and inactive phases of their disease. No significant protective effect was observed from the presence of RF.

Several studies have suggested that rheumatoid factor (RF) protects against the development of renal disease in patients with systemic lupus erythematosus (SLE).^{1–3} This is not universally accepted, however.^{4–6} In the main, previous studies have used only the classical Rose-Waaler or latex tests. These tests detect IgM rheumatoid factor, but not IgG or IgA, and it would seem important to assess the role of all three isotypes. We have therefore, investigated the possible protective effect using both a standard latex test and the more sophisticated technique of radioimmunoassay (RIA), which identifies IgG, IgA, and IgM isotypes of rheumatoid factor. Previous authors have analysed their lupus patients in simple groups, for example 'renal' versus 'non-renal', but this does not allow for the important factor of disease activity at the time the patients were studied. In this study we assessed rheumatoid factor in the following patient groups: (a) patients with SLE and renal involvement, tested during active and inactive phases of renal disease (n=26); (b) patients with SLE and no renal involvement (n=25); and (c) patients with idiopathic nephritis, and no evidence of autoimmune rheumatic disease (n=21).

Patients, materials and methods

PATIENTS

Each of the patients with SLE had four or more of the 1982 revised American Rheumatism Association criteria for the classification of SLE.⁷ Twenty six patients with SLE were considered to have renal involvement because three or more of the following had been present at some stage of their illness: diastolic hypertension (fourth phase sound >90 mmHg), oedema requiring diuretic treatment not due to any other obvious cause, proteinuria >0.5 g/24 h, creatinine clearance <60 ml/min, or raised plasma creatinine concentration >124 µmol/l.

In 22 of these patients the serum was studied during an active phase of their disease. Renal disease was considered to be active in the presence of a rising diastolic blood pressure, rising plasma or urine creatinine concentrations during a two month period, casts or red blood cells, or both, on urine microscopy, or a renal biopsy showing active inflammation. Serum samples were taken from 16 patients at follow up when they had no evidence of active disease. In addition, four serum samples were studied during inactive disease only. Patients with SLE and no renal involvement were selected on the basis of their having been followed up for several years without any evidence of the features listed above. The 21 patients with idiopathic renal disease had focal and diffuse glomerulonephritis (GN) (four patients), proliferative GN (six), membranous

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Correspondence to Dr L Turner-Stokes, Department of Rheumatology, 3rd Floor, Arthur Stanley House, Tottenham Street, London W1P 9PG.

GN (two), mesangial proliferative GN (two), focal GN (one), or IgA nephropathy (six).

MATERIALS AND METHODS

Rheumatoid factor was assayed by slide latex test in addition to RIA, which was carried out as follows.⁸ Ninety-six-well flexible plates were coated with 100 µl of 10 µg/ml human Fc in phosphate buffered saline (PBS) and incubated for one hour at 37°C. After washing, the plates were blocked with 0.4% bovine serum albumin (BSA) for two hours at 37°C and washed again in cold PBS. Serum samples were diluted 1/100 in PBS/0.5% Tween/0.4% BSA and incubated in 100 µl aliquots for a further hour at 37°C before washing in cold PBS. The different isotypes of rheumatoid factor were detected by incubating rabbit antihuman IgM (Dako), IgA (Dako), or Fd of human IgG (5 µg/ml in PBS/0.5% Tween/0.4% BSA) for one hour at 37°C. Bound immunoglobulin was labelled with 5 µg/ml ¹²⁵I goat antirabbit IgG in PBS/0.5% Tween for one hour. After washing, the plates were counted in a Packard crystal multidetection system. Results were expressed as nanograms of ¹²⁵I goat antirabbit IgG bound. Upper limits of normal ranges were set at the mean +2SD of a normal healthy population (n=70); in this case IgM RF 27 ng, IgG RF 35 ng, and IgA RF 75 ng. The anti-IgM and anti-IgA antiserum (Dako) were both absorbed on a human IgG column and shown to be specific using purified IgM, IgA, and IgG on the plate. Anti-Fd of IgG was specific for the Fab region of the heavy chain of IgG. Dithiothreitol treatment of serum abolished all IgM RF activity without any effect on the IgA or IgG RF assay. Similarly, no difference was found in the concentrations of RF when pepsin treated antisera were compared with the whole antiserum.

STATISTICS

Results were analysed by the χ^2 statistical test.

Results

Table 1 shows the number of patients in each group with positive rheumatoid factor (RF), measured by slide latex test and RIA. Although 7/25 (28%) of the patients with SLE without renal lupus were RF positive by latex test as opposed to 2/26 (8%) with renal disease, this was not statistically significant. Furthermore, by RIA more patients with SLE and renal disease had RF (6/26 (23%)) than those without (4/25 (16%)), though the concentrations found were low. In the SLE subgroup with renal disease no differences were found by latex or RIA (IgM, IgG, or IgA) between the active and inactive disease groups. IgG and IgA were very infrequently

Table 1 Number of patients in each group measured by slide latex test and radioimmunoassay

Patient group (n)	Latex (>1/40)	IgM RF (>27 ng)	IgG RF (>35 ng)	IgA RF (>75 ng)
SLE with no renal disease (25)	7	4	—	—
SLE with renal disease (26)	2	6	—	2
Active (22)	1	3	—	1
Inactive (20)	1	3	—	1
Idiopathic renal disease (21)	—	2	—	1

detected and only 2/21 (10%) of the patients with idiopathic renal disease had IgM RF (by RIA).

Discussion

A protective role for rheumatoid factor in the pathogenesis of lupus nephritis was first suggested by Davis and Bollet.¹ Demonstration of the reactivity of rheumatoid factor with soluble antigen-antibody complexes to form more heavily sedimenting immune precipitates⁹ has led to speculation that its role may involve formation of less soluble complexes, easily phagocytosed and thus less likely to deposit in the renal glomeruli. Since then there have been a number of conflicting reports concerning this protective role (see Table 2).

There are a number of possible reasons for the disparity between reports. Firstly, it could reflect differences in assay methods, especially as the concentrations of RF in these patients with SLE are low. Most authors employed aggregation tests using either latex particles or red blood cells. Varying results were obtained with either method, and it seems unlikely, therefore, that this accounts for the observed differences, especially as Hill *et al* demonstrated a protective role in their series using both assays.

A recent report from Helin *et al* once again found a protective effect, and suggested that differences in patient material could account for the discrepancies, such as the proportion of rheumatoid factor positive patients (21% in their series).³ A survey of our own patients with SLE showed a similar proportion—26/100 (26%)—with a positive rheumatoid factor (>1/40 by slide latex test). Variable activity of renal disease could also account for the observed differences, however.

16 Turner-Stokes, Jones, Addison, Mansell, Isenberg

Table 2 Reports on the protective role of rheumatoid factor in the development of lupus nephritis

Author	SLE defined	No with SLE	Renal disease defined	No with renal disease	Active/inactive phase studied	Assay method	Protective effect (p value)
Davis and Bollet ¹	Not specified	35	Clinical	23	No	Not specified	<0.001
Kantor <i>et al</i> ⁴	Clinical	51	Not specified	24	No	Latex	NS
Baldwin <i>et al</i> ⁵	Clinical + ANF* or LE cells	82	Biopsy	27	No	Latex >1/80	NS
Hill <i>et al</i> ²	1971 ARA* criteria ¹¹	59	Biopsy	59	No	Latex >1/80 Rose-Waaler >1/32	=0.05–0.1 <0.05
Helin <i>et al</i> ³	1982 ARA criteria ⁷	52	Clinical ± biopsy (in 29)	35	No	Rose-Waaler >1/64	<0.005
Pinillos <i>et al</i> ⁶	1982 ARA criteria	78	Clinical ± biopsy (in 38)	40	No	Rose-Waaler >1/64	NS
Tarkowski and Westberg ¹⁰	1982 ARA criteria	51	Clinical	25	Yes	EIA* IgG IgA IgM	<0.001 <0.05 <0.05
Present study	1982 ARA criteria	51	Clinical ± biopsy (in 19)	26	Yes	Latex >1/40 RIA* IgG IgA IgM	NS NS NS NS

*ANF=antinuclear factor; ARA=American Rheumatism Association; EIA=enzyme linked immunoassay; RIA=radioimmunoassay.

To address these possibilities we studied patients both in active and inactive phases of their disease, and in addition to the standard latex test we used an RIA technique, which distinguishes the three isotypes of rheumatoid factor. Our results show that although a trend towards a protective role for rheumatoid factor against the development of renal disease was seen by the latex test, this was not statistically significant. Furthermore, analysis by RIA showed no protection at all. In addition, activity of the lupus nephritis made no difference.

Very recently Tarkowski and Westberg measured rheumatoid factor isotypes by enzyme linked immunoassay and reported a protective role for all three, especially for IgG.¹⁰ They suggested that by competing with complement for binding with immune complexes, and thus minimising their injurious properties, IgG RF could be more protective than IgM. Against this however, was the correlation of active disease with the presence of IgM rheumatoid factor isotypes in their study.

The protective role for rheumatoid factor against the development of nephropathy in SLE remains contentious. The failure of two recent studies to show a correlation with disease activity suggests, however, that its pathogenetic role can at best be small.

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